Actas Dermosifiliogr. 2010;**101(3)**:197-200

ACTAS
Dermo-Sifiliográficas

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OPINION ARTICLE

Antioxidants in Photoprotection: Do They Really Work?

Antioxidantes en fotoprotección, ¿realmente funcionan?

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Before answering the question of whether antioxidants have photoprotective properties, most clinical dermatologists would like to know if they are capable of blocking ultraviolet (UV) radiation or if they increase the sun protection factor (SPF) of topical sunscreens. The concept of photoprotection is so closely linked to the use of topical sunscreens that they are sometimes understood to be one and the same, even though the noxious effects of solar radiation apart from erythema include immunological disturbances, DNA damage, activation of stress proteins, increased levels of reactive oxygen species (ROS), and reduction of the effectiveness of antioxidant systems.

Comparisons of the degree of protection between topical sunscreens and antioxidants on the basis of SPF is a mistake, as their level of activity in photoprotection is very different. SPF is calculated on the basis of the ability to prevent erythema through the application of a given substance, and serves to measure the effectiveness of topical sunscreens that basically act by blocking the effects of the most erythematogenic form of UV radiation—namely UVB rays. However, antioxidants act by blocking or repairing oxidative processes such as lipid peroxidation, the modification of structural proteins and damage to DNA that are basically generated by UVA radiation. Their capacity for blocking UVB rays is very limited and will therefore not prevent the appearance of erythema, such that their effectiveness cannot be measured by their minimal SPF. However, antioxidants can act as photoprotectors in the broadest sense of the word—denoting any substance capable of preventing sun-induced skin damage—as they protect the skin from damaging intermediate cellular and molecular processes that topical sunscreens with a very high SPF are unable to prevent. This action is even more important when we consider that human skin receives 10 times more UVA than UVB radiation.

Oxidative Stress

In aerobic organisms oxidative processes occur as a consequence of the natural consumption of oxygen. Oxygen is normally found in its most stable form, but certain situations, such as the use of tobacco or alcohol, inflammatory processes, ionizing radiation, and above all exposure to UV radiation can produce ROS that are highly reactive and can damage the skin through oxidation. Free radicals within the ROS are particularly harmful because the presence of an unpaired electron makes them highly unstable and gives them a tendency to pair with electrons from other molecules in order to become stable. This action damages the other molecule and the DNA, and, more importantly, stealing the electron creates another free radical which also seeks to stabilize itself by attacking yet another molecule, provoking a chain reaction.

ROS formation is promoted by the presence of metal ions, released in tissue damaged by UV radiation. The ions act as catalysts in the production of ROS through the Fenton reaction (hydroxyl radical [OH^-] formation through the interaction of hydrogen peroxide [H_2O_2] with iron or copper ions, for example).

In optimal situations the organism has antioxidant systems capable of neutralizing physiologically generated ROS, but in pathological situations, and especially under

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the effect of UV radiation, an imbalance is created between ROS production and antioxidant systems that are no longer capable of halting the oxidative processes. This provokes oxidative stress and leads to multiple reactions that eventually result in cell damage.

ROS damage a large number of molecular structures. Lipids undergo lipid peroxidation presumably mediated by singlet oxygen, leading to the destruction of membranes. UVA radiation is implicated to a greater degree in this process than UVB is, and short exposures to UVA have been shown to produce lipid oxidation markers such as malonaldehyde and 4-hydroxynonenal in fibroblasts, and lipid hydroperoxides in keratinocytes.

At the protein level, ROS intervene in the oxidation of thiols, presumably mediated by singlet oxygen. Consequently, the proteins are denatured as their quaternary structure and finally their enzymatic systems are altered. In vivo studies show that keratin is rapidly oxidized, and biomarkers of oxidative damage such as N-lysine increase with chronic photoexposure.[1]

The oxidation of carbohydrates also causes cell damage through the formation of carbonyl groups, leading to premature glycan production.

The main targets of free radicals are the nucleophilic sites and the nitrogenated bases of DNA, which can lead to DNA cross-links and breaks. The most important oxidative effects of ROS on DNA include base modification, especially in the generation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG), a substance with high mutagenic potential.[2] Another consequence of free radical attacks on DNA is the breaking of strands with cleavage of the phosphodiester bond. H_2O_2 and the superoxide anion have also been shown to induce the activation of certain oncogenes under experimental conditions.

Free Radicals and Carcinogenesis

ROS has been implicated in all stages of carcinogenesis (initiation, promotion, progression, and metastasis).[3,4]

OH^- forms in oxidative processes through the Fenton reaction. As explained above, OH^- alters the bases of cellular DNA, initiating tumor development.

The signal that antioxidants have been consumed leads to the release of calcium, which promotes tumors by 2 mechanisms: the direct activation of protooncogenes such as c-Fos and the indirect effects on transcription factor phosphorylation by calcium-dependent protein kinase.[5]

Tumor progression is encouraged by the loss of immune vigilance and genomic instability derived from oxidative stress, and by the reduction of antioxidant systems.

Finally, ROS promote the liberation of proteases by endothelial cells and this contributes to tumor metastasis.[6] There have also been descriptions of ROS accelerating angiogenic processes encouraging the dissemination of tumor cells.[7]

Natural Antioxidant Systems

Natural antioxidant systems are basic components of protective processes that maintain the correct balance between the production and elimination of ROS and other related molecules. According to Halliwell and Gutteridge,[8] an antioxidant is defined as any substance that, when present at concentrations that are lower than those of an oxidizable substrate, will significantly delay or prevent oxidation of that substrate.

Natural antioxidants are the main defense mechanism against oxidative damage in human beings as they counteract the harmful effects of ROS.

Natural antioxidants may be broadly classified as enzymatic or nonenzymatic, the latter being of low molecular weight. Within the enzymatic group, there are protective systems that are synthesized within the cells. Examples are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). Other enzymatic antioxidants are found in the extracellular fluid. Examples are ceruloplasmin, transferrin, or haptoglobin. The most important nonenzymatic antioxidant systems are glutathione, ascorbic acid (vitamin C), alpha tocopherol (vitamin E), and the carotenoids.

Antioxidants can act in 3 ways: a) some (albumin, ferritin, ceruloplasmin, transferrin) prevent the formation of free radicals, b) others (SOD, GPx, catalase) carry out endogenous repair of damage caused by free radicals and c) still others (vitamin E, vitamin C, beta-carotene, flavonoids) scavenge for free radicals.

Amongst the dietary antioxidants, those with most impact on the skin are alpha tocopherol, the carotenoids (both of which are liposoluble and have great capacity for protection against lipid peroxidation in cell membranes), and ascorbic acid, which acts as a cofactor for various enzymes.

The levels of antioxidants in the skin are higher in sun exposed areas. The epidermis has 5 times more ascorbate than the dermis.[9] Furthermore, the amount of ferritin is greater in keratinocytes than in fibroblasts due to the anatomical location of each.[10]

Antioxidants as Photoprotectors

There are many studies on the effect of antioxidants in the prevention of cutaneous erythema, although, as was commented above, the range of antioxidant action is practically the same as the UVA action spectrum (320 to 400 nm), meaning the photoprotective potential of these substances is determined by protection against molecular and DNA damage derived from UV-induced oxidative stress, not merely protection from sun-induced erythema.

The scientific community is currently sensitive to the impact of oxidative stress in all areas of health and, as UV radiation is known to be the most effective factor in inducing oxidative damage to skin cells, active antioxidant substances are being sought for topical and systemic applications.

Vitamin E

Vitamin E is one of many antioxidant substances with photoprotective effects. It has a high impact on lipid

peroxidation, interrupting the chain of free radicals by donating a single hydrogen atom to the lipid radical or peroxide. It is constantly regenerated by the fundamental action of vitamin C and glutathione serving as cofactors in the repair of UV-induced damage.[11-14]

Many studies show topical application of vitamin E to be effective in the prevention of sun-induced erythema of the skin[15-17] and several sources report further increases in photoprotection from a combination of vitamin E and vitamin C.[18,19] Furthermore, repeated combined application following exposure to sun radiation has been shown to delay reaction to the minimal erythema dose by up to 26%, clearly demonstrating that these antioxidants are capable of providing protection from erythema independently of their ability to absorb UV radiation.

Betacarotenes

The betacarotenes have been used as systemic photoprotective agents in the treatment of porphyria. Their antioxidant effect comes from their ability to protect against actinic erythema, as they act against the free radicals generated by UV radiation.[20]

Green Tea Polyphenols

Camelia sinensis (a green tea) is a plant rich in polyphenols such as catechins and phenolic acids. The main antioxidant of green tea is epigalocatechin-3-gallate, which has a proven photoprotective effect as it delays UV-induced cutaneous erythema by reducing levels of H_2O_2 in the epidermis and dermis following irradiation.[21] Its antioxidant properties were shown to be capable of inhibiting carcinogenesis in mice with UV-induced cutaneous carcinoma.[22] Green tea extracts have also been shown to reduce induction of p53 and apoptotic keratinocytes in UVB irradiated human skin.[23]

Polypodium leucotomos

Oral or topical administration of *Polypodium leucotomos* can provide strong antioxidant, anti-inflammatory, immune and photoprotective effects. The antioxidant mechanism is based on this agent's ability to deactivate singlet oxygen and scavenge for free radicals. It has a preventive effect against sun-induced erythema, reducing the number of sunburn cells and preventing damage to DNA.[24]

P. leucotomos is also noted for its immune protective action against UV-induced immune suppression, as it blocks the depletion of Langerhans cells following exposure to sunlight[25] and inhibits the photoisomerization of trans-urocanic acid to its cis form.[26]

Resveratrol

Resveratrol is found in *Vitis vinifera* (grape). The main active compounds are found in the seed and skin of the fruit.

This compound has strong antioxidant properties and proven photoprotective capacity in the prevention of solar erythema. It is currently widely used for its antiaging effects, the result of activation of sirtuin-1, which in turn encourages the transcription of DNA repair genes and antioxidant enzymes, such as SOD, while suppressing the transcription of proapoptotic genes, such as the BIM gene.[27]

Recent research has examined a series of antioxidant substances with photoprotective capabilities such as the theaflavins of black tea, amino acids of the mycosporine type derived from algae, Pycnogenol, Lycopan, caffeine, or ubiquinone.[28-32] Many of these are used in cosmetics to delay photoaging and there is a current tendency to add topical sunscreens to antiaging creams.

Skin photoprotection is also evolving and recent recommendations for broad-spectrum sunscreens with a critical wavelength of 380 nm[33] mean the use of topical sunscreens must not be exclusively limited to UVB blockers. In 2006, the European Union recommended that sunscreens should give UVA protection of at least a third of the SPF and stressed that the concept of total protection should not be associated solely with the use of topical sunscreens.

Novel photoprotective measures proposed have included the use of DNA repair enzymes or light-refracting microspheres capable of optimizing the effectiveness of sunscreens. The concept of photoprotection is changing and we must understand that integrated photoprotection should include the prevention of UV-induced oxidative damage. Priority must therefore be placed on strengthening natural antioxidant systems and investigating antioxidant substances capable of counteracting the damaging effects of ROS for topical or systemic applications.

Conflicts of Interest

The authors declare no conflicts of interest.

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